

U.S.S.N. 09/776,533

Filed: February 7, 2001

RESPONSE AND AMENDMENT TO OFFICE ACTION

months, to and including February 6, 2003, along with the required fee. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

In the Specification

Please replace the paragraph on page 11, lines 10-19, with the following paragraph.

B1 These antibodies can be further modified by the use of PHARMACIA'S® (PHARMACIA® LKB Biotechnology, Sweden) "Recombinant Phage Antibody System" (RPAS), which generates a single-chain Fv fragment (ScFv) which incorporates the complete antigen-binding domain of the antibody. In the RPAS, antibody variable heavy and light chain genes are separately amplified from the hybridoma mRNA and cloned into an expression vector. The heavy and light chain domains are co-expressed on the same polypeptide chain after joining with a short linker DNA which codes for a flexible peptide. This assembly generates a single-chain Fv fragment (ScFv) which incorporates the complete antigen-binding domain of the antibody.

Please replace the paragraph on page 12, lines 13-16, with the following paragraph.

B2 The peptides can also be conjugated to a carrier protein such as keyhole limpet hemocyanin by its N-terminal cysteine by standard procedures such as the commercial IMJECT® kit from Pierce Chemicals or expressed as a fusion protein, which may have increased efficacy.

Please replace the paragraph on page 15, lines 20-25, with the following paragraph.

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B3 Examples of molecular modeling systems are the CHARMM® and QUANTA® programs, Polygen Corporation, Waltham, MA. CHARMM® performs the energy minimization and molecular dynamics functions. QUANTA® performs the construction, graphic modeling and analysis of molecular structure. QUANTA® allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other.*A*

Please replace the paragraph on page 19, lines 13-26, with the following paragraph.

B4 Methods to produce or synthesize oligonucleotides are well known in the art. Such methods can range from standard enzymatic digestion followed by nucleotide fragment isolation (see e.g., Sambrook et al., Chapters 5, 6) to purely synthetic methods, for example, by the cyanoethyl phosphoramidite method using a Milligen or BECKMAN® System 1Plus DNA synthesizer (see also, Ikuta et al., in *An. Rev. Biochem.*, 1984 53, 323-356 (phosphotriester and phosphite-triester methods); Narang et al., in *Methods Enzymol.*, 65, 610-620 (1980) (phosphotriester method). Accordingly, DNA sequences of the 5' flanking region of the integrin protein gene described herein can be used to design and construct oligonucleotides including a DNA sequence consisting essentially of at least 10 to 15 consecutive nucleotides, with or without base modifications or intercalating agent derivatives, for use in forming triple helices specifically within the 5' flanking region of a integrin protein gene in order to inhibit expression of the gene.-

Please replace the paragraph on page 20, lines 8-16, with the following paragraph.

B5 Carrier materials for direct administration include biodegradable materials, such as a synthetic polymer degrading by hydrolysis, for example, polyhydroxy acids like polylactic acid,

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polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, proteins such as gelatin and collagen, or carbohydrates or polysaccharides such as cellulose and derivatized celluloses, chitosan, alginate, or combinations thereof. Other materials include block copolymers of polyoxyethylene (PLURONICS®, BASF®) or the diacrylate block copolymers described by Hubbell, et al, in U.S. Patent No. 5,567,435 issued on October 22, 1996.

Please replace the paragraph on page 20, lines 17-21, with the following paragraph.

A6

The use of biodegradable matrices eliminates the need for surgery to remove implanted materials. However, synthetic non-biodegradable matrices may also be used. Useful materials include ethylene vinyl acetate, polyvinyl alcohol, silicone, polyurethane, non-biodegradable polyesters, and tetrafluoroethylene meshes (TEFLON®).

Please replace the abstract of the application with the following paragraph.

B7

Compounds that specifically inhibit or reduce leukocyte adhesion or function are useful to enhance vascular healing and lessen restenosis of blood vessels after revascularization, via angioplasty or bypass surgery, of diseased coronary, peripheral and cerebral arteries, and lessen stenosis or restenosis of surgically-placed bypass grafts and transplanted organs. Examples of these compounds are those which block cell surface integrins, such as Mac-1 (CD11b/CD18, αMβ2) or their ligands. Both superficial and deep injury was significantly reduced with treatment using an antibody to Mac-1 compared to both saline controls and IgG controls in the examples. After balloon angioplasty (superficial injury) neointimal area was reduced nearly 70%. The ratio of intimal:medial area was reduced over 75%. After endovascular stent implantation (deep injury) neointimal area was reduced nearly 40%. Extrapolated to humans,